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Original Paper

Can the Published Data Tell Us About the Effectiveness of Neoadjuvant Chemotherapy for Locally Advanced Cancer of the Uterine Cervix?

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The effect of neoadjuvant chemotherapy on survival of patients with locally advanced cervical cancer was investigated by conducting a systematic review and meta-analysis of the published data. Of the 21 randomised trials that we identified, only 15 were published. Furthermore, 2-year survival data could be extracted from only seven trial reports and 3-year survival from only nine trial reports. Meta-analyses of the published data at 2 and 3 years are neither clearly in favour of neoadjuvant chemotherapy nor control (2 years: odds ratio (OR) = 1.09, 95% confidence interval (CI) = 0.83–1.45, $P = 0.37$; 3 years: OR = 0.96, 95% confidence interval (CI) = 0.73–1.25, $P = 0.45$). Being restricted to only some of the data from a relatively small fraction of the randomised trials, these analyses potentially suffer from a number of biases and are therefore inconclusive. The only reliable way to judge the value of neoadjuvant chemotherapy in this disease is to perform a meta-analysis of centrally collected, updated, individual data on all patients from all known randomised trials. Such an analysis is currently being carried out by an international collaborative group. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

RADICAL RADIOTHERAPY comprising external beam irradiation with brachytherapy is the preferred treatment for locally advanced cervical cancer (International Federation of Gynecology and Obstetrics, FIGO stage IIB, III and IVA). It is also used frequently instead of surgery in the treatment of FIGO IB bulky (barrel-shaped) tumours. By targeting the cervix, paracervix and sites of potential regional spread, this treatment provides a good chance of cure; 5-year-survival has been reported as being as high as 64% for stage IIB [1], but in stage IVA disease, 5-year survival can be very poor at around 17% [1].

Neoadjuvant chemotherapy offers the potential to reduce tumour volume, thereby facilitating primary radiotherapy or surgery. In addition, it may serve to control micrometastatic disease and so improve survival. The high response rates reported for cisplatin-based regimens in phase II studies reviewed in [2], led to randomised trials comparing neoadjuvant cisplatin-based combinations plus primary treatment with primary treatment alone. Most of the published randomised trials have been small and inconclusive. This is not surprising because most recruited fewer than 250 patients, and as a result, they had generally less than 40% power to detect a 10% difference in 5-year survival. Although the individual trials may have insufficient numbers of patients to detect moderate survival benefits with reliability, the combination of the results of these trials in a meta-analysis might give sufficient statistical power to help decide whether neoadjuvant chemotherapy is beneficial in the treatment of locally advanced disease. Therefore, we aimed to identify all trials of neoadjuvant therapy for locally advanced cervical cancer and carry out a meta-analysis of the published trials.

PATIENTS AND METHODS

All trials were sought that randomly assigned patients with locally advanced cervical cancer (FIGO Stage 1B bulky, IIB-IVA) to receive neoadjuvant chemotherapy or no neoadjuvant chemotherapy in addition to the same local treatment

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(surgery, radiotherapy or both). Published trials were initially identified by systematic searches of Medline and CancerLit (using the optimum search strategy developed by the Cochrane Collaboration [3]) and by examination of the reference lists of the trial publications and review articles. Trial registers (Cochrane Controlled Trials Register, UK Coordinating Committee on Cancer Research Register of Cancer Trials and Physicians Data Query) were also consulted to help identify other trials. Based on theses searches, 21 potentially eligible trials were identified, encompassing over 2000 patients. Ten of these were published as full papers [4–13], five as abstracts [14–18] and six are currently unpublished, one of which is still ongoing (Table 1).

A meta-analysis of 2- and 3-year survival using the available published data was carried out. Figures for 2- and 3-year survival were either extracted from the text or estimated from the published survival curves of the most recent trial report (Table 1) and analysed using the methods described below [19]. The numbers at risk were adjusted (reduced), where appropriate, and if possible, to allow for immature follow-up [20]. The overall numbers of deaths in each trial were not used to calculate an odds ratio (OR), because not all trial publications reported the overall number of deaths, and the length of follow up varied considerably amongst those that did. If such an analysis had been performed, the calculated OR for each trial would be based on a different point in time and so the combination of these in a meta-analysis would be difficult to interpret.

For each trial, at each timepoint, the OR was calculated from the number of patients at risk and the observed number of deaths on each arm ($OR = \exp[(O_t - E_t)/V]$) where O_t is the observed number of deaths in the treatment arm, E_t is the expected number of deaths in the treatment arm under the hypothesis of no difference and V is the variance. In the case of $E_t(N_t(O_t + O_c)/N)$ and $V(E_t(1 - N_t/N)(N - O_t - O_c)/N - 1)$, the observed number of deaths on control is O_c, the number of patients randomised to treatment is N_t and the total number of patients randomised is N. The confidence intervals (CIs) for each OR were calculated using the expression $\exp(O_t - E_t)/V \pm \gamma/\sqrt{V}]$, where γ takes the values 1.96 and 2.58 for the 95% and 99% intervals, respectively. The ORs for individual trials were combined across all trials to produce an overall OR ($\exp[\Sigma(O_t - E_t))/\Sigma V]$) and the associated 95% CIs ($\exp[\Sigma(O_t - E_t)/\Sigma V \pm 1.96/\sqrt{\Sigma V})$) for each timepoint [21].

RESULTS

Of the 21 eligible trials, 15 were published in some form. Three trial reports [6, 12, 13] and the five abstracts [14–18] either did not quote 2-year survival or did not include survival curves. Therefore, the analysis was based on only seven out of fifteen published trials (350 deaths, 937 patients). Some OR estimates for individual trials were in favour of neoadjuvant chemotherapy and others were in favour of local treatment alone (Figure 1), but the 95% CIs were very wide and only one demonstrated a conventionally significant result in favour of neoadjuvant treatment [7]. Much of the statistical heterogeneity ($\chi^2 = 15.65$, df = 6, $P = 0.02$) was contributed by this trial and this heterogeneity became much reduced when the trial was removed from the analysis ($\chi^2 = 5.82$, df = 5, $P = 0.32$). Combining the estimates, the six trials gave an overall OR of 1.09 (95% CI = 0.83–1.45), which is neither clearly in favour of neoadjuvant chemotherapy nor control ($\chi^2 = 0.80$, df = 1, $P = 0.37$).

Table 1. *Characteristics of identified trials*

Author [ref.]	Comparison	Stage	Patients randomised (analysed in publication)	Median or minimum–maximum follow-up (years)
Cardenas [14]	CT + RT versus RT	IIIB	29 (28)	2.9
Chauvergne [4]	CT + RT versus RT	IIB–Ni, III, M0	195 (172)	5.0–10.0
Kumar [5]	CT + RT versus RT	IIB–IVA	184 (184)	1.8–2.5
Kumar [15]	CT + RT versus RT	IIIB	?	?
Leborgne [7]	CT + RT versus RT	IB–IVA (IB > 4 cm)	97 (97)	?
Sardi [16]	CT + RT versus RT (versus CT + S)	IIIB	101 (101)‡	2.1
Sardi [7]	CT + RT (± S) versus RT (± S)	IB bulky	210 (205)	5.6
Sardi [17]	CT + RT versus RT (versus s + RT versus CT + S)	IIB	145 (145)‡	7.0
Souhami [8]	CT + RT versus RT	IIIB	107 (91)	3.7–4.3
Sundfor [9]	CT + RT versus RT	IIIB–IVA	96 (94)	3.7–3.8
Symonds [18]	CT + RT versus RT	II–IVA	215 (204)	1.0–3.0
Tattersall [10]	CT + RT versus RT	IIB–IVA	71 (71)	?
Tattersall [11]	CT + RT versus RT	IIB–IVA	260 (260)	1.3
FNCLCC COII*	CT + RT versus RT	IIB, IIIB	180§	–
GOG 14†	CT + S and/or RT versus S and/or RT	IB bulky	340§	–
LGOG*	CT + local treatment versus local treatment	locally advanced	27	–
MRC CTO (CECA)*	CT + RT or S versus RT or S	IB–IVA	48	–
PMB Group*	CT + RT versus RT	bulky IB, II–IVA	35	–
WGH, Edinburgh (C1)*	CT + RT versus RT	IIB, IIIB	100§	–
Chiara [12]	CT + RT + CT versus RT	IIB–III	64 (61)	3.0
Tobias [13]	CT + RT + CT versus RT	inoperable IIA, IIB, III–IVA	178 (90)	?

*Unpublished; †Ongoing; ‡Refers to relevant treatment arms only; §Target accrual.

Three-year survival data could not be extracted from the reports of six of the published trials [5, 6, 13–15, 17] and so the analysis was based on only nine of fifteen published trials (416 deaths, 988 patients). Again, the estimated ORs varied across the individual trials (Figure 1), the 95% CIs were wide and there was a single trial that was significantly in favour of neoadjuvant treatment [7]. Although the overall OR (0.96, 95% CI = 0.73–1.25) was neither in favour of neoadjuvant chemotherapy nor control ($\chi^2 = 0.56$, df = 1, $P = 0.45$), there was substantial statistical heterogeneity ($\chi^2 = 23.65$, df = 8, $P = 0.003$). As in the analysis of 2-year survival, the extreme results of a single trial [7] seemed to be the main cause.

DISCUSSION

Our searches identified 15 published, five unpublished and one ongoing trial comprising around 2000 patients. However, both of our analyses were limited to part of the data from only a fraction (47–60%) of the published randomised trials, and so potentially suffer from publication bias. Other biases may have been introduced, because the trial publications did not necessarily report on all randomised patients (see Table 1) and the extent of follow-up was variable. Further, there was an unacceptably high level of statistical heterogeneity in the both the 2- and 3-year survival analysis. Another problem is that fixed timepoint analyses give no indication of the overall survival experience on neoadjuvant treatment versus control.

There may be sufficient randomised evidence to assess whether neoadjuvant chemotherapy can improve survival in locally advanced cervical cancer. However, many of the known trials are unpublished and even in the published reports data are limited. Therefore, it does not seem possible to judge the value of this treatment either qualitatively or quantitatively on the basis of the scarce data available in the medical literature. Despite this, a recent qualitative review [22] (which cited only nine of the fifteen published trials) made the recommendation that neoadjuvant chemotherapy should not be used as a standard treatment for locally advanced cervical cancer.

The only reliable way to address this question is to collect updated individual data on all patients from all the randomised trials described, and to combine the results in an appropriate time-to-event analysis, stratified by trial. This should provide the most unbiased, up-to-date estimate of the average effect of neoadjuvant chemotherapy and, with approximately 2000 patients, we should have at least 90% power ($\alpha = 0.05$) to detect a 10% difference in survival (e.g. from 65 to 75% in stage II disease and 40 to 50% in stage III

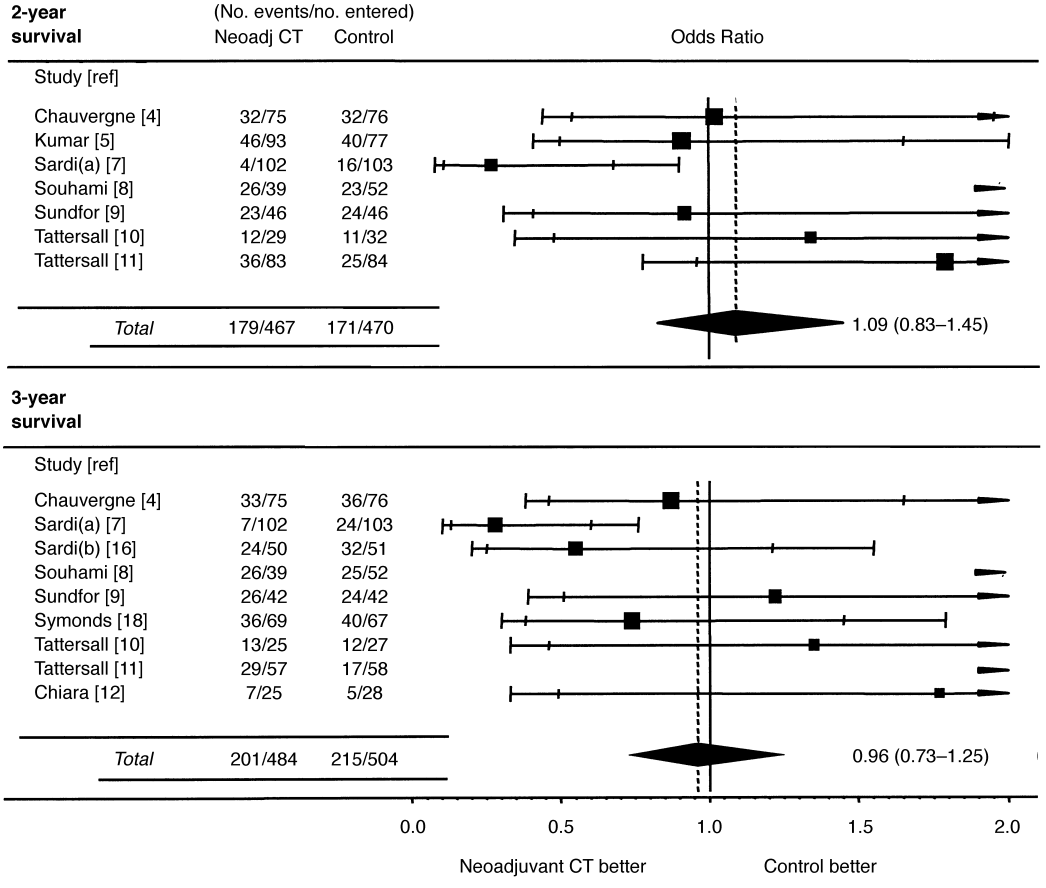

Figure 1. Meta-analysis, at 2 and 3 years, of published randomised trials of neoadjuvant chemotherapy for locally advanced cervix cancer. The odds ratio (OR) for each trial is represented by the centre square on each bar, the size of which is directly proportional to the amount of information available in the trial. The inner and outer limits of the bar indicate the 95 and 99% confidence intervals (CIs), respectively. The line drawn through the OR value of 1.0 indicates no difference between the treatment arms. An OR to the left of this equivalence line suggests an advantage for neoadjuvant chemotherapy and an OR lying to the right suggests an advantage for control. If the 95% CI for a trial crosses this line then the results did not reach significance at the 0.05 level. The black diamond gives the overall OR when the results of all trials were combined and the extremes of the diamond give the 95% CI. Note that sometimes the numbers at risk were adjusted (reduced) to allow for immature follow-up.

disease). In addition, by collecting data on recurrence and baseline patient characteristics, it is possible to explore the biological effect of neoadjuvant chemotherapy and whether any effect of neoadjuvant chemotherapy is consistent across, for example, different stages or grades of disease. We have, therefore, initiated an international collaborative meta-analysis to collect and analyse these data.

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